URETHANE*
CAS No. 51-79-6
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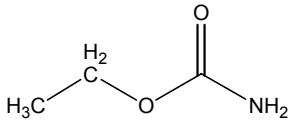

CARCINOGENICITY

Urethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC V.7, 1974; IARC S.4, 1982; IARC S.7, 1987). When administered in the drinking water, urethane induced lung adenomas, lymphomas (mainly lymphosarcomas), liver angiomas and hemangiomas, papillomas, sebaceous carcinomas of the skin, harderian gland tumors, pulmonary adenomas, squamous cell tumors, mammary carcinomas, and malignant mesenchymal tumors of the fat pad in mice of both sexes; malignant lymphomas, hemangiomas or hemangiosarcomas of the liver, spleen, or uterus, hepatomas, adrenal cortex adenomas, and fibrosarcomas of the mesentery or uterus in female rats; and papillomas, squamous cell carcinomas of the forestomach, malignant lymphomas, mammary tumors, hepatomas, hemangiomas or hemangiosarcomas of the liver, melanotic skin tumors, pulmonary adenomatosis, and adenomatous polyps of the cecum in hamsters of both sexes. When administered by gavage in water followed by topical applications of croton oil, urethane induced an increase in skin papillomas and lung adenomas in mice of both sexes. When administered by gavage in dioctyl ester of sodium sulfosuccinic acid, urethane induced lymphocytic leukemias, stomach papillomas, hepatomas, and pulmonary adenomas in male mice. When applied topically followed by applications of croton oil solution in acetone or when administered in conjunction with dimethylbenz[*a*]anthracene (DMBA), urethane produced skin tumors in mice of both sexes. When administered by inhalation in aerosol sprays (pressure and ultrasonic), urethane induced adenomas and solid squamous tumors in mice of both sexes. When injected subcutaneously postpartum in a gelatin suspension, urethane induced both thymic and malignant lymphomas and pulmonary adenomas in newborn mice of both sexes. When injected subcutaneously, urethane induced leukemia in mice in both sexes. A continuation of these studies also revealed the influence of age as a factor in the susceptibility of the liver to urethane carcinogenesis; hepatomas occurred rapidly among all groups treated neonatally with urethane. When injected subcutaneously, urethane induced melanotic lesions of the iris in newborn rats of both sexes, and adrenal cortical tumors, ß-cell tumors of the pancreatic islet cells, forestomach papillomas, lung and intestinal tumors, dermal melanocytomas, and thyroid tumors in newborn hamsters of both sexes. When injected intraperitoneally, urethane induced adenomas in female mice; increased incidences of mammary tumors, Zymbal gland carcinomas, angiomas and sarcomas at various sites, malignant lymphomas, kidney tumors, and epidermal cysts in rats of both sexes; increased incidences of leukemia in male and female newborn mice; malignant lymphomas, lung adenomas, harderian gland tumors, and stromal and epithelial ovarian tumors in rats of both sexes; neoplasms, embryonal kidney tumors, harderian gland adenomas, and Anitschkow cell sarcomas of the heart in both newborn and adult rats of both sexes; and

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* The name urethane is sometimes applied to high-molecular weight polyurethanes used as foams, elastomers, and coatings. Such products are not made from the chemical urethane and do not generate it upon decomposition.

melanotic tumors in male and female newborn hamsters. When injected intraperitoneally in distilled water, urethane induced an increased incidence of hepatomas in partially hepatectomized and nonhepatectomized male mice (IARC V.7, 1974). When injected intraperitoneally in sodium chloride followed by a second injection of butylated hydroxytoluene (BHT) in corn oil, urethane induced increased incidences of alveolar and papillary tumors of the lung in neonatal mice of both sexes (Beer & Malkinson, 1985). When injected intraperitoneally or intravenously to female mice before parturition, urethane induced an increased incidence of lung tumors in both sexes of offspring. Subcutaneous injections of urethane to pregnant female mice resulted in enhanced development of hepatomas, ovarian tumors, and pulmonary adenomas in the mothers. When injected intraperitoneally to pregnant female rats, urethane induced hepatomas and sarcomas of the heart in the offspring. When injected subcutaneously, urethane induced pulmonary adenomas in suckling offspring of mice of both sexes. Urethane also enhanced the leukemogenic effect of X-irradiation in mice. X-irradiation combined with administration of urethane led to the induction of mammary carcinomas in mice (IARC V.7, 1974).

There are no data available to evaluate the carcinogenicity of urethane in humans.

PROPERTIES

Urethane may occur as a colorless, odorless columnar crystals or a white, granular powder. It is slightly soluble in olive oil and soluble in water, ethane, ether, glycerol, chloroform, and ethyl ether. When heated to decomposition, it emits toxic fumes of nitrogen oxides (NO_x). Urethane is available in the United States as an N.F. grade in the form of a fused solid or crystals that contain 99.43% active ingredient. It may react with strong oxidizers.

USE

According to EPA, urethane is not currently being used for commercial purposes due to its potent toxicity. The small quantities being sold are most likely for research purposes. Historically, the primary use of urethane has been as a chemical intermediate in preparation of amino resins. The process involved a reaction with formaldehyde to give hydroxymethyl derivatives that are used as cross-linking agents in permanent press textile treatments designed to impart wash-and-wear properties to fabrics (IARC V.7, 1974). Urethane has also been utilized as a solubilizer and co-solvent in the manufacture of pesticides, fumigants, and cosmetics; as an inactive component or solubilizer in liquid preparations for injections; and in biochemical and pharmacological research and in human and veterinary medicine. In the past, urethane was used as an active ingredient in drugs prescribed for the treatment of neoplastic diseases, as a sclerosing solution for varicose veins, as a hypnotic, and as a topical bactericide. For all of these medicinal uses, successful substitutes have been found and are being used today. Its commercial use in pharmaceuticals stopped in June 1983. In addition, two anticonvulsant drugs, trimethadione and paramethadione, can be contaminated with urethane. The allowable limit has been set at 1 ppm. These anticonvulsant drugs may be used only to treat epilepsy that is refractory to other available drugs (CHIP, 1979d).

PRODUCTION

The 1986 Chem Sources USA directory identified one domestic producer of urethane (Chem Sources, 1986). According to EPA, as of 1984, urethane was no longer being produced commercially in the United States There are no known importers of urethane. It appears that only very small quantities (research quantities) are being sold. The 1979 TSCA Inventory identified five companies producing 6.1 million lb of urethane in 1977 with some site limitations (TSCA, 1979). U.S. companies have produced urethane commercially since 1945 (IARC V.7, 1974).

EXPOSURE

The primary routes of potential human exposure to urethane are inhalation, ingestion, and dermal contact. When released to soil or water it is expected to adsorb only weakly and to leach to ground water. In atmosphere it will either be washed out by rain or react with photochemically produced hydroxyl radicals (half-life 2.2 days). Formerly, patients treated with pharmaceuticals containing urethane were potentially exposed through injection. Reports of possible human exposure to urethane are not available. Potential human exposure to urethane may occur during its production or use in medical research. Certain epileptic patients may potentially be exposed to urethane as a result of its presence as a contaminant in the anticonvulsant drugs, trimethadione and paramethadione. Consumers were potentially exposed to urethane residues in textiles treated with the compound. Investigators have found urethane in dimethyl pyrocarbonate-treated beverages and in wine, beer, orange juice, and some soft drinks. Urethane also has been found to occur in foods not treated with dimethyl pyrocarbonate but made by a fermentation process, including ale, beer, bread, wine, soy sauce, yogurt, and olives (IARC V.7, 1974; CHIP, 1979d). The Toxic Chemical Release Inventory (EPA) listed three industrial facilities that produced, processed, or otherwise used urethane in 1996 (TRI, 1999). In compliance with the Community Right-to-Know Program, the facilities reported releases of urethane to the environment which were estimated to total 12538 lb.

REGULATIONS

EPA regulates urethane under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource, Conservation and Recovery Act (RCRA), Superfund Amendments and Reauthorization Act (SARA), and Toxic Substances Control Act (TSCA). A statutory reportable quantity (RQ) of 1 lb was established for urethane, but EPA increased the RQ to 100 lb under CERCLA. RCRA subjects the chemical's waste products, off-specification batches, and spill residues to handling and report/recordkeeping requirements. Urethane is subject to reporting rules under SARA and TSCA. FDA has prohibited the use of urethane in drugs and food. OSHA regulates urethane under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-149.